



Direction for Basal Insulin Therapy by Once Daily Injection in the Clinical Practice

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Received date: 06 January 2021; **Accepted date:** 10 February 2021; **Published date:** 17 February 2021

Citation: Bando H. Direction for Basal Insulin Therapy by Once Daily Injection in the Clinical Practice. Diab Res Open Access. 2021 Feb 17;3(1):11-15.

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Abstract

American Diabetes Association (ADA) has announced the new version of the standards of Medical Care in Diabetes-2021. The guideline of the diabetic patients with Older Adults seems to be used for a wide range of clinical practice. Among them, several impressive comments were found, where “Once-daily basal insulin injection therapy is associated with minimal side effects and maybe a reasonable option in many elder patients”. Recent topic includes Dual Action of Liraglutide and insulin degludec (DUAL) studies, and Xultophy has shown beneficial efficacy. Consequently, the trend would be developed from multiple daily injection (MDI) method to once daily injection.

Keywords

American Diabetes Association (ADA), Dual Action of Liraglutide and Insulin Degludec (DUAL) studies, Xultophy, Multiple Daily Injection (MDI), Once Daily Injection

New Year 2021 has come. On January 1, American Diabetes Association (ADA) has announced the new version of the standards of Medical Care in Diabetes-2021 [1]. It has 16 chapters with 222 pages. Among them, chapter 12 was for the guideline of the diabetic patients with Older Adults. In the actual medical practice, many elderly diabetic patients have been increased and treated [2]. The usual medical management for elder diabetic patients requires an adequate assessment of medical, functional, psychological, and social aspects, which means biopsychosocial domains [3]. Then, the treatment guideline for them would be the most common problem. From the current situation, several useful and impressive information will be introduced in this

article.

Firstly, Diabetes has been highly prevalent for the elderly population. In >65 years old, more than one-quarter of adults show diabetic and one-half of them show prediabetes. Diabetic condition has a close relationship with geriatric syndromes, including cognitive impairment, depression, persistent pain, falls, urinary incontinence, and polypharmacy. These problems usually aggravate QOL and self-management (level B) [4].

Lifestyle management included the recommendation of optimal nutrition and protein intake [5], aerobic activity, weight-bearing exercise, resistance training.

Furthermore, several intensive lifestyle interventions should be considered such as dietary changes, physical activity, and weight reduction about 5-7%. These can be beneficial on QOL [6], physical functioning and mobility [7], and cardiometabolic risk factor control [8] (level A).

Secondly, the crucial points of pharmacological therapy recommendations include i) select oral hypoglycemic agents (OHA) with low risk of hypoglycemia, ii) avoid overtreatment common in elder diabetic adults [9], iii) make simplification of complex regimens [10], iv) consider necessary costs of care and insurance coverage for developing therapeutic plans.

For OHA, metformin is the first-line agent, which can be safely provided when $eGFR \geq 30 \text{ mL/min/1.73m}^2$. Dipeptidyl peptidase-4 inhibitor (DPP-4i) has a low reverse effect such as hypoglycemia but rather expensive [11]. Sodium 2 Glucose Cotransporter 2 Inhibitors (SGLT2i) are beneficial for cardiovascular disease, heart failure, and CKD progression [12]. Glucagon-like peptide 1 receptor agonists (GLP-1Ra) are beneficial for patients with established cardiovascular disease [13]. Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial showed the improved outcomes when cases are >50 years with CVD (HR 0.83) [14]. In contrast, cases >60 years with no CVD showed various adverse events observed, such as nausea, vomiting, and diarrhea (HR 1.20).

Thirdly, several beneficial treatment protocols concerning insulin therapy will be described [2].

- 1) Concerning the insulin therapy, rather a breakthrough comment was found. "Once-daily basal insulin injection therapy is associated with minimal side effects and maybe a reasonable option in many older patients". Multiple daily injections (MDI) of insulin may be too complex for the older patient, who has already advanced complications, coexisting chronic illnesses, or impaired functional status. The insulin regimen is recommended to become more simply protocol. The Algorithm is shown for an adequate insulin regimen for older T2DM. Basal insulins include

glargine U-100, U-300, detemir, degludec and human NPH [15]. For better glucose variability, titrate dose of basal insulin on average fasting fingerstick data over a week. The goal is 90-150 mg/dL (5.0-8.3 mmol/L) [1].

- 2) An important comment is found for mealtime insulin. If mealtime insulin is >10 units/dose, decrease dose 50% and add noninsulin agents. If it is ≤ 10 units/dose, discontinue mealtime insulin and add noninsulin agents. After that, adequate management includes the evaluation of the estimated glomerular filtration rate (eGFR). When $eGFR \geq 45 \text{ mL/min/1.73m}^2$, start metformin 500mg daily and increase dose every 2 weeks. When $eGFR < 45 \text{ mL/min/1.73m}^2$, diabetic patient has been already on metformin, or metformin is not tolerated, proceed to the second-line OHA [16].
- 3) Some additional tips are included. When adjusting mealtime insulin, use simplified sliding scale. If premeal glucose >250 (<350) mg/dL, provide 2(4) units of short- or rapid-acting insulin. Stop sliding scale method when not needed daily [2].

Fourthly, three patterns of patient status were classified, which are i) healthy, ii) complex/intermediate and iii) very complex/poor health [17]. Treatment goals of HbA_{1c}, fasting glucose and blood pressure are shown as follows.

- 1) Healthy: It shows intact cognitive and functional status with longer remaining life expectancy, where 7.0-7.5%, 80-130 mg/dL, 140/90 mmHg with statin (unless contraindicated or not tolerated).
- 2) Complex/intermediate: It shows multiple coexisting chronic illnesses, mild-to-moderate cognitive impairment, hypoglycemia vulnerability and fall risk. The target points are 8.0%, 90-150 mg/dL, 140/90 mmHg with statin (unless contraindicated or not tolerated).
- 3) Very complex/poor health: It shows moderate-to-severe cognitive impairment [18] or ADL impairments, associated with uncertain benefit for life expectancy. Avoid reliance on HbA_{1c} value, and diabetic management is based on avoiding hypoglycemia and symptomatic

hyperglycemia. The target goal includes 100-180 mg/dL, 150/90 mmHg with the consideration of possible benefit with statin. For diabetic patients with mild cognitive impairment (MCI), the trial of intranasal insulin and metformin therapy had provided insights for future developing studies [19].

From mentioned above, recent topic includes the changes from MDI method to once daily injection as possible. The background to this would be the spread of basal insulin and the clinical application of Xultophy as a combination of insulin and GLP-1Ra. It is Insulin Degludec/Liraglutide (IDegLira, Xultophy) which is a fixed-ratio combination (FRC) for convenient and useful clinical efficacy [20]. There were a series of Dual Action of Liraglutide and insulin degludec (DUAL) studies on Xultophy. DUAL ii Japan was conducted for phase 3a randomized treat-to-target trial for half year [21]. The results revealed that the mean HbA1c/weight reduction was 1.6%/1.5kg, respectively for 6 months. Another study for Xultophy (n=413) showed that HbA1c change for 6 months was -0.16% as basal HbA1c <9%, and -1.67% as basal HbA1c ≥9%, respectively [22]. Furthermore, BMI showed -0.46% for those with less than 30, and -0.75% for those 30 or more than 30. Authors have reported the effects of Xultophy for patients with diabetes and chronic renal failure [23,24]. The useful add-on therapy (AOT) to diabetes would be useful for future treatment for diabetes with the satisfaction of patients [25].

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Manuscript no: DROA-3-11-15

Volume: 3 Issue: 1

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